Osteoporosis Clinical Trial Design: Regulatory History

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Osteoporosis Guidance 1994

- Preclinical studies: “no detrimental effect on bone quality (including bone histology, density and strength)” in 2 species
- Clinical data:
  - Normal bone quality (biopsy) in a subset of pts at 3 yr
  - BMD ↑ “statistically and clinically significant”
  - Positive trend ($p<0.2$) in 3-year fracture data, with “no deterioration in the third year”
  - Fracture study must continue (post-marketing) to “5 years or as needed to show fracture reduction”

Phase 3 clinical trial design

- ≥ 3-year, randomized, double blind
- Placebo or active control
- Primary endpoint: new morphometric vertebral fx
- Other efficacy endpoints:
  - clinical fractures (each major type and combined all types)
  - BMD
  - bone turnover markers

Treatment of PMO phase 3 trials since 1994 Guidance

- Placebo-controlled, 3 years (except teriparatide)
- Primary endpoint: lumbar spine BMD (supportive fx data)
  - Alendronate (approved 1995), FIT ongoing
- Primary endpoint: new morphometric vertebral fx
  - Raloxifene (approved 1999)
  - Risedronate (2000)
  - Teriparatide (2002)
  - Ibandronate (2003)
  - Zoledronic acid (2007)
  - Denosumab (2010)

Trial duration

Trial Duration: Etidronate

	Lumbar spine BMD % change from baseline	
	Year 2	**Year 3**
Etidronate	4.9	5.1
Placebo	1.5	1.0
	New vertebral fractures % of subjects	
	Year 0 → 2	**Year 2 → 3**
Etidronate	6.7	11.3
Placebo	12.1	10.7
Am J Med 1993; 95:557		

PMO fracture trials: Vertebral fracture efficacy by year

	Absolute Risk Reduction (%) vs. placebo		
Year (cumulative)	**Year 1**	**Year 2**	**Year 3**
Etidronate	-	5.4	3.1*
Alendronate (FIT-1)	-	7.2	7.0
Risedronate (VERT-NA)	4.0	5.9	5.0
Risedronate (VERT-MN)	7.7	13.1	10.9
Ibandronate	0.6*	2.3	3.7
Zoledronic acid	2.2	5.5	7.6
Denosumab	1.4	3.5	4.8

*NS. Sources: Prescribing information (RIS, ZOL, DEN); *Lancet 1996,348:1535* (ALN); *JBMR 2004, 19:1241* (IBD); *Am. J. Med. 1993, 95: 557* (ETID)

PMO fracture trials: Vertebral fracture efficacy by year

	Relative Risk Reduction (% vs. placebo)		
Year (cumulative)	**Year 1**	**Year 2**	**Year 3**
Etidronate	-	44	18*
Alendronate (FIT-1)	-	62	47
Risedronate (VERT-NA)	65	55	41
Risedronate (VERT-MN)	61	59	49
Ibandronate	58*	61	62
Zoledronic acid	60	71	70
Denosumab	61	71	68

*NS. Sources: Prescribing information (RIS, ZOL, DEN); *Lancet 1996,348:1535* (ALN); *JBMR 2004, 19:1241* (IBD); *Am. J. Med. 1993, 95: 557* (ETID)

PMO fracture trials: Non-vertebral fracture efficacy by year

	Relative Risk Reduction (% vs. placebo)		
Year (cumulative)	**Year 1**	**Year 2**	**Year 3**
Alendronate (FIT-1/2)	15	26	26
Risedronate (VERT-NA)	41	35	38
Risedronate (VERT-MN)	15	37	32
Zoledronic acid	16	23	25
Denosumab	16	21	20

JCEM 2000, 85:4118 (ALN); *JAMA* 1999, 282:1344 and *Osteoporos Int* 2000, 11:83 (RIS); *NEJM* 2007, 356: 1809 (ZOL); *NEJM* 2009, 361:756 (DEN)

Trial Duration

- Current approach: vertebral fracture efficacy can be demonstrated in 2 years for most drugs
- Longer periods may be needed to evaluate hip fractures, depending on sample size
- A trial duration of 2 or 3 years will not adequately address questions regarding potential long term safety concerns

Active control trials

Are placebo-controlled osteoporosis trials still appropriate?

- Declaration of Helsinki 2002: placebo unethical if effective therapy exists and use of placebo may lead to serious or irreversible harm
- FDA AC meeting 2002: Placebo-controlled trials are still appropriate/ feasible in many circumstances
  - Many women with PMO don't receive/ cannot tolerate existing treatments
  - All trial participants receive calcium/vitamin D supplements
  - Discontinuation option for subjects with new fracture or bone loss

Placebo-controlled osteoporosis trials: Lower-risk study populations

- Exclude women with multiple/severe/recent vertebral fx or hip fx
- Relative risk reductions are similar between high-risk and moderate-risk pts (e.g. FIT-1 and FIT-2)
  - fracture data can be extrapolated across risk groups
- Larger trials
- Powered for nonvertebral and hip fractures
- > 90% outside U.S.

Active-control trials

- Superiority or non-inferiority (NI)
- If NI: must be adequate background documentation of the reproducible efficacy of the active control in the study population
- Active-test difference greater than a “clinically significant threshold” should be ruled out by confidence interval analysis
- 1994 Guidance: no recommendations on the choice of active control or the NI margin

Active Control BMD Trials

- BMD generally acceptable as primary endpoint for supplemental trials of approved drugs with fracture efficacy; BTMs supportive
    - New formulations or dosing regimens
    - BMD non-inferiority at 1 year
        - NI margins based on maintaining a prespecified fraction of the treatment effect of the original regimen/formulation
- BMD alone is not acceptable for comparative efficacy claims (either superiority or NI) between two approved drugs; fracture data is needed

Active-control fracture trials

- Appropriate for high-risk or moderate-risk pts
- Superiority:
  - anabolic vs. antiresorptive
- Non-inferiority:
  - drugs in same class

Active-control fracture trials: Non-inferiority

- Very large sample sizes needed
  - probably feasible for vertebral fractures
  - not feasible for hip fractures
- Assay sensitivity uncertain
  - placebo-controlled fx data (e.g. in moderate-risk pts) may be preferred over non-inferiority fx data (e.g. in high-risk pts)
  - potential advantages of a new drug (e.g. safety, convenience) should also be considered

Thank you